ADVANCES IN THE RADIOTHERAPY OF SKIN CANCER

BY

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CERTIFICATION

I certify that this thesis has not already been submitted for any degree and is not being submitted as part of candidature for any other degree.

I also certify that the thesis has been written by me and that any help I have received in preparing this thesis have been acknowledged in this thesis.

Dr G B Fogarty

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ABBREVIATIONS

3DCRT, 3D	Three dimensional conformal radiotherapy
ASM	Annual Scientific Meeting
BCC	Basal cell carcinoma
CNS	Central nervous system
cSCC	Cutaneous squamous cell carcinoma
CT	Computed tomograph
Dmax	Depth of the maximum dose for a megavoltage beam
DNA	Deoxyribose Nucleic Acid
DSMC	Data safety monitoring committee
EGFR	Epidermal growth factor receptor
eGFR	Estimated glomerular filtration rate
EGFRI	Epidermal growth factor receptor inhibitor
EORTC	European Organisation for Research and Treatment of Cancer
EORTC BN-20	EORTC Quality of Life Questionnaire with Brain module
EORTC QLQ-C30	EORTC Quality of Life Questionnaire
EPI	Electronic portal imaging
ERA	Excellence in Research for AustraliaInitiative
GDS	Global Deficit Scores
HDRBT	High Dose Rate Brachytherapy
HRQOL	Healthrelated quality of life
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
IVRS	Interactive voice response system
KPS	Karnofsky Performance Scale
MC1R	Melano Cortin -1- Receptor
MCC	Merkel cell carcinoma
MLCs	Multileaf collimators
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
MUs	Machine monitor units
NBCCS	Nevoid basal cell carcinoma syndrome
NCF	Neurocognitive function
NSW	New South Wales
PET	Positron Emission Tomography

PMCC	Peter MacCallum Cancer Centre
PORT	Postoperative radiotherapy
QA	Quality assurance
RA	RapidArc®
RANZCR	Royal Australian and New Zealand College of Radiologists
RCTs	Randomised clinical trials
RHC	Red Hair Colour
RT	Radiotherapy
SCC	Squamous cell carcinoma
SIB	Simultaneous integrated boost
SNP	Single nucleotide polymorphisms
SRS	Stereotactic radiosurgery
UV	Ultraviolet
VMAT	Volumetric Modulated Arc Therapy
WBRT	Whole brain radiotherapy

GLOSSARY OF SPECIALIST MEDICAL TERMS FOR LAY PERSON

- Acute effects – side effects of radiotherapy that occur during treatment delivery or up to 3 months post treatment . These effects are dominated by acute inflammation.
- Adjuvant treatment – a treatment that assists the main treatment in eradicating cancer. Often it assists the definitive or main treatment e.g. chemoradiotherapy – the chemotherapy makes the radiation more effective.
- Axilla – anatomical term for region of the armpit.
- Cancer– a condition whereby cells divide uncontrollably, forming malignant tumours that can invade into other parts of the body.
- Chart – record of patient medical history.
- Definitive treatment – the main treatment being used to eradicate cancer. Adjuvant treatments assist the definitive treatment.
- Immunosuppression–a condition with decreased immunity. This is associated with increased skin cancer risk in older Caucasians living in climates of high ultra violet (UV) exposure.
- Late effects – side effects of radiotherapy that occur at least 6 months after treatment delivery. These effects are dominated by chronic inflammation with the laying down of fibrosis and consequent loss of organ elasticity.
- Megavoltage radiotherapy – radiation for treatment produced by linear accelerators capable of high generating voltages. The possibility of skin sparing is common with this modality.
- Melanoma – type of skin cancer that metastasizes early.
- Metastasis– or secondary; cancer that has spread from the primary and is not continuous with primary.
- Multidisciplinary care – when more than one modality or craft group is employed in treatment , e.g. surgery and radiotherapy.
- Non-melanoma skin cancer – skin cancer that is not melanoma. These include basal cell or cutaneous squamous cell carcinoma. Other more uncommon non-melanoma skin cancers are primary skin lymphomas and merkel cell carcinoma.
- Occult primary – a cancer diagnosed with secondaries that has no identifiable primary lesion.

- Palliative treatment – treatment that aims to increase quality rather than quantity of life. This treatment is usually given for the relief of a specific cancer symptom e.g. pain.
- Primary – the original cancer from which metastases or secondaries arise.
- Radical treatment – when the treatment intent is cure or at least increasing survival. Treatment side effects are tolerated for this end.
- Radiobiology– the study of the action of ionizing radiation on living things.
- Radiotherapy – ionizing electromagnetic energy used in medicine for treating pathology, usually cancer.
- Secondary – or metastases – cancer that has spread from the primary and is not continuous with primary.
- Skin cancer– cancers that have their origin in the epidermis and dermis of skin, the visible covering of the body.
- Skin sparing –property of megavoltage radiation that means that the maximum dose is not at the skin surface.
- Supraorbital – anatomical term for region above the eye.
- Synergistic treatments – when the combination of both treatments gives more tumour control that when the same treatments are used individually.
- Therapeutic ratio – ratio of tumour cell kill to normal tissue side effects. The aim of all cancer treatment is to maximize this ratio – more tumour kill for less normal tissue toxicity.
- Triage – the process by which cases of differing risks are prioritized for treatment.

THESIS PROJECTS BY CODE AND SHORT TITLE IN EACH CHAPTER

CHAPTER 1: Introduction

CHAPTER2: Molecular Advances

2.1 EGFR in skin SCC

2.2 MC1R Skin effects

2.3 Skin Tumour gene.

CHAPTER3: Advances in Radiation Techniques

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3.2 RT of Supraorbital Nerve

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3.5 Skin RT techniques Fall

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4.2.3 RT in recurrent BCC

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4.2.4 Rituximab and skin SCC

4.2.5 Radiation Recall

EXECUTIVE SUMMARY

The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world. Twenty four projects were selected from the total works of the candidate, the majority being first in world reports. The projects are groupedaccording to whether their advances are in the molecular area, are a radiation technique, are advances in the clinical area, in quality assurance or guidelines area. Most projects owe their origin to astute observation of unexpected findings in the clinic. Project quality is high as measured by citations, Impact Factor of the journals in which they are published and inclusion in the ERA 2012 Journal List. These projects were either practice changing or confirming in their time. As the thesis develops there is a growing momentum of the underlying importance of the need for communication, for personalized treatment of skin cancer with radiotherapy and for clinical vigilance. This thesis provides a platform for further research and a significant resource for future health workers.

ABSTRACT

Introduction

The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

Methodology

Twenty four projects that led to publication over a ten year period by the candidate were selected. They were selected because they were on the subject of radiotherapy of skin cancer and represented a new advance. An essay was written linking them together so as to highlight the findings of each individual project and to investigate and discover common underlying themes.

Results

The quality of the projects is high as they have been published in peer reviewed journals with respectable impact factors. A number have been significantly cited in subsequent articles and open access publications have received significant hits. Most have been published in journals on the ERA 2012 Journal List.

The specific reasons why each project was investigated included:

- the desire for self audit
- to find an association
- to investigate unexpected findings
- to create much needed guidelines
- to compare treatments and techniques.

The specific reasons for publishing included:

- to inform on unexpected results
- to inform on expected but never before published results
- to suggest new guidelines
- to disseminate knowledge on new techniques
- to invite collaboration in a specific trial
- as part of a controversy.

The linking essay comprises six chapters that deals with advances:

- on the molecular level
- in radiation techniques
- in clinical areas
- in quality assurance
- that suggest new guidelines

Significant underlying themes found were:

- the need for communication
- the need for personalized treatment of skin cancer with radiotherapy
- the importance of clinical vigilance.

Conclusions

This thesis shows that radiotherapy in skin cancer has a real place. It describes specifically how the selected projects led to significant advances in the radiation treatment of skin. The thesis provides a significant resource for future health workers. It also provides a platform for further radiotherapy research into improving skin cancer patient outcomes. This thesis will hopefully be a stimulus to other Australian radiation oncologists to engage in this important subspecialty.

OVERVIEW

This thesis is about advances in radiotherapy in skin cancer. The main purpose of the thesis is to highlight the important role that radiotherapy has in the treatment of skin cancer. This is critically important in Australia which has the highest burden of skin cancer in the world.

There are two main components for assessment in this thesis. The first and major component is made up of projects that have led to peer-reviewed publications. Significant work occurred during the candidature. The second component is a reflection on these advances. This reflection is in the form of a linking essay that introduces and integrates the projects. The reflection comments on the advances in the radiation treatment of skin cancerinvestigated and published by the candidate in the last ten years.

Twenty four projects were selected from the total published works of the candidate. The majority are first in world literature reports aiding their successful passage through peer review. These projects were either practice changing or confirming, in their time.
These projects were selected according to the following criteria:

a. They are relevant to the radiation treatment of patients with skin cancer.
b. They represent an advance in skin cancer treatment – they are either a new discovery or new way of integrating current technology in the skin cancer setting.
c. They have been deemed worthy of publication by peers so that this information may be made available to other physicians involved in the care of skin cancer patients

All the projects attempted to enhance the therapeutic ratio of treatment for the benefit of patients in the present and of the future. Most projects owe their origin to astute observation of unexpected findings in the clinic. The projects were usually initiated by the candidate. The specific reasons why each project was investigated included the desire for self audit, to find an association, to investigate unexpected findings, to create much needed guidelines and to compare treatments and techniques. The specific reasons for publishing included: to inform on unexpected results, to inform on expected but

never before published results, to suggest new guidelines, to disseminate knowledge on new techniques, to invite collaboration in a specific trial and as part of a controversy.The quality of the projects is high as they have been published in a peer reviewed journals. A number have been significantly cited in subsequent articles and open access publications have received significant hits. Most have been published in journals on the ERA 2012 Journal List, which have respectable Impact Factors.

The sevenchapters of the thesis include as chapter one an introduction that sets out the purpose of the thesis and sets the scene by a focused literature review. The basis of radiation is explained, especially the ability to conserve in-field normal tissue. The therapeutic ratio has been shown to be a useful tool to evaluate advances.

Chapters two to five describe the contribution to the thesis of projects according to whether their advances are in the molecular area, are radiation techniques, are advances in the clinical area or the quality assurance and guidelines area. This classification is arbitrary but does reflect where the projects impact clinical practice. Chapter six outlines significant ongoing projects that occurred during the candidate's doctoral candidature and concern a randomized trial for Whole Brain Radiotherapy (WBRT) in melanoma and the provision of cutting edge modern technology to the radiotherapy care of skin patients.

Chapter two focuses on the molecular basis of radiation for skin cancer. Molecular changes are the most fundamental in any living system and determine the outcome at more macroscopic levels. The first project (*2.1*) shows it is necessary to confirm the existence of the target in the cells requiring treatment before embarking on a full study of a targeted cancer agent in skin cancer. The second study (*2.2*) found that the difference in frequency of alleles encoding a 'Red Hair Colour' (RHC) phenotype in the cohort of patients with unexpectedly severe acute skin radiation reactions (n=12) was significantly increased compared to the control population (p=0.003) and was especially associated with the R160W variant allele [odds ratio =3.64 (95% CI:1.3-10.27)]. This discovery could potentially contribute to a predictive assay for normal tissue damage from RT. The third project (*2.3*) may have been the first description of a new tumour

suppressor gene syndrome with multiple BCCs in previously irradiated fields, multiple cancers and multiple immunological disorders in the same patient. These projects were all world first reports.

Chapter three comprises techniques developed in an era of three dimensional conformal radiotherapy (3DCRT). They all lead to greater conformality of the radiation dose cloud to the target, often by use of lateral thinking. The axilla project (*3.1*) shows that fields applied with no knowledge of where the tumour is, and what dose to use, leads to poor outcomes. The second project (*3.2*) shows that new technology is not always necessary for better conformality. What is needed is to know the volume requiring radiation and the limits of the current tools. The third project (*3.3*) details how two eyes were saved by thinking laterally about eye position during definitive radiotherapy for skin cancer in cooperative patients. The last three projects (*3.4-3.6*) detail techniques written with radiation therapists from other countries in mind. These projects were all world first reports except the second which was a reply to a previous publication, creating a controversy.

Chapterfour comprises projects relating to clinical advances and these are among the most frequently cited in the thesis. The chapter has two parts. The first is about imaging and comprises three projects about staging. From a study of 100 melanoma patients (*4.1.1*), it was found that staging magnetic resonance imaging (MRI) brain was only needed if patients already had Stage IV disease, had symptoms that may have come from a cerebral secondary, or were contemplating significant treatments for which the finding of an incidental brain metastasis would have made that treatment inappropriate. The next project (*4.1.2*) showed that astute thinking resulted in finding that a PET scan, which diagnosed a melanoma patient as having stage IV disease, actually had a warthin's tumour causing a false positive. The last imaging study (*4.1.3*) found that PET does not add significantly to finding occult primary tumours in 21 cases of patients who presented with cervicallymphadenopathyoverthat given by careful clinical, endoscopic, and radiological examinations. All these projects show that imaging is helpful but not a replacement of the basic clinical skills of proper history taking and examination.

The second part of this chapter consists of projects that examine the interaction of other

anti-cancer treatments with radiotherapy. The initial three projects were about interactions with surgery. The first project (*4.2.1*) describes a case of complete reversal of neurological symptoms following haemorrhage into a cerebral melanoma metastasis with palliative surgery rather than immediate WBRT. The second project (*4.2.2*) found that a delay in postoperative radiotherapy (PORT) for cSCC, BCC and MCC was associated with a worse outcome in ten of 330 patients who had to wait longer than our unit benchmarks. The third project (*4.2.3*) describes what can happen when PORT is not offered for a positive perineural deep margin following resection of a large BCC of the back. The patient developed spinal cord compression that was salvaged by RT. The last two projects concern chemotherapy. The first project (*4.2.4*) describes activation and rapid progression of cSCC in three Caucasians, with long histories of sun damaged skin, following administration of Rituximab. The second project (*4.2.5*) was the third case report in the world literature of a radiation recall reaction with Gemcitabine and the first about radiation recall myositis. The key point of this chapter is that clinicians need to know the relevant place of each diagnostic and therapeutic modality and cannot be just an isolated expert in their own.

Chapter five examines quality assurance (QA) issues and guidelines of radiation treatments for skin cancer. Three QA projects are about the QA of treatment process. The first (*5.1*) is an audit of a chart round review which showed that completion rate of items that were regarded as necessary for effective treatment increased from 80 to 99% with the institution of the chart round. The second project (*5.2*) details a similar audit of a chart round review in a skin radiotherapy unit. The third project (*5.3*) is an invited review of the importance of peer review in QA in the first edition of an international textbook; the candidate was the only Australian contributor. Two projects were presented under guidelines. Guidelines are produced by recognized experts. They are a summary of experience from providers of new advances to new providers of those advances. In project *5.4* the candidate assisted with the updating of the National Guidelines as the evidence-based consensus for skin cancer radiation practice in Australia. Project *5.5* clarified to referrers when referral of a skin cancer patient to a skin multidisciplinary clinic which included radiotherapists was appropriate. Studying how advances are applied through QA completes the journey from idea to safe routine clinical practice. The development of guidelines then makes these advances available

for new practitioners in other departments to apply them safely and in a standard and comparable fashion, an important consideration for dissemination of new advances throughout the industry and for standardization in collaborative ongoing multicenter research.

Chapter six outlines projects that occurred during the candidate's doctoral candidature and are ongoing. Project *6.1* will provide evidence for WBRT in melanoma. At this stage WBRT is given or withheld in melanoma on the basis of no specific randomized evidence. Project *6.2* will strengthen the case to provide cutting edge modern technology to the radiotherapy care of skin patients.

Chapter seven summarises and concludes the thesis, and gives direction for further research.

Recurring themes throughout of the thesis have been:

1. The need for communication within and without the multidisciplinary team.
2. The need for personalized treatment of skin cancer with radiotherapy, given the great variety of patient, tumour and treatment factors.
3. The importance of clinical vigilance.

The contributions of the projects to these themes have been commented on in each chapter. There has been a growing momentum of the underlying importance of these themes in the radiotherapy care of patients with skin cancer as the thesis develops.

This thesis provides a significant resource to health workers involved in the radiation treatment of patients with skin cancer. It also provides a platform for further research into improving skin cancer patient outcomes. It shows that radiotherapy in skin cancer has a real place and this thesis will be a stimulus to other Australian radiation oncologists to engage in this important subspecialty. As Australia has the highest incidence of skin cancer in the world, spends the majority of its cancer budget on skin cancer and has rising incidence and mortality from this group of diseases, it is only fitting that Australia plays a leading role in advancing the radiation treatments available for skin cancer.